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ABSTRACT BOOK

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The Role of Hydrogen Sulfide

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BACKGROUND: Hydrogen sulfide (H_2S) has also been shown to protect the heart in the setting of ischemia/reperfusion injury. We investigated the therapeutic potential of H_2S donors, in preclinical models of heart failure. We evaluated the effects of chronic H2S therapy on myocardial contractile function, vascular density and angiogenesis. Studies were also performed to determine the molecular and cellular mechanisms by which H2S protects the heart during heart failure.

METHODS AND RESULTS: Transverse aortic constriction was performed in mice (C57BL/6J; 8-10 weeks of age). Mice received either vehicle or H_2S donor drugs starting 24 hours after transverse aortic constriction and were followed for up to 12 weeks using echocardiography.
H_2S therapy with H_2S donors significantly improved left ventricular remodeling and preserved left ventricular function in the setting of transverse aortic constriction. H_2S therapy increased the expression of the proangiogenic factor, vascular endothelial cell growth factor, and decreased the angiogenesis inhibitor, angiostatin. Further studies revealed that H_2S therapy increased the phosphorylation of endothelial NO synthase and the bioavailability of NO. Importantly, these changes were associated with an increase in vascular density within the H_2S -treated hearts. In additional studies we determined that H_2S therapy resulted in the activation of endothelial nitric oxide synthase (eNOS) via phosphorylation of serine^{1177} and increased nitric oxide (NO) bioavailability. Interestingly, we determined that eNOS was uncoupled in CSE KO mice with reduced levels of H_2S and NO coupled with an exacerbated injury response to acute myocardial infarction.

CONCLUSIONS: These results suggest that H_2S therapy attenuates left ventricular remodeling and dysfunction in the setting of heart failure by creating a proangiogenic environment for the growth of new vessels. A major mechanism related to these cytoprotective actions is the activation of eNOS and increased nitric oxide bioavailability.

Nutrition and cardiovascular disease

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Several studies have suggested that fruits and vegetables might protect against the development and progression of cardiovascular disease, one of the leading causes of morbidity and mortality worldwide. In this context, the vascular endothelium has been often suggested – or proven – to be the main target of *functional foods* and *nutraceutics*. The vascular endothelial cell plays a pivotal role in arterial homeostasis. Reduced nitric oxide (NO) bioavailability is a consequence of endothelial dysfunction and believed to represent the earliest step in the pathogenesis of atherosclerosis. Concordantly, endothelial dysfunction/damage has been indicated as an important and independent predictor of future development of cardiovascular risk and events. In addition, probably also because of the role of NO in modulating insulin sensitivity, an impaired NO bioavailability has been commonly described in patients with metabolic syndrome.
Thus, endothelial dysfunction has been also suggested as a contributor to the onset of insulin resistance.

The association between brachial NO-dependent flow-mediated dilation (FMD) and cardiovascular disease risk has been investigated in several prospective studies, suggesting that FMD is inversely associated with future cardiovascular events. Dietary flavonoids have been described to improve endothelial function and FMD. A proposed mechanism by which dietary flavonoids could affect FMD is that they improve the bioactivity and bioavailability of the endothelium-derived vasodilator NO by enhancing NO synthesis or by decreasing superoxide-mediated NO breakdown.
This could be of clinical relevance and may suggest a mechanistic explanation for the reduced risk of cardiovascular events and stroke observed in consumers of fruits and vegetables in a number of studies.

In keeping to the above, we investigated in various subsets, including control subjects and essential hypertensive patients, the effects of flavanol-rich dark chocolate administration on FMD, wave reflections, blood pressure, endothelin-1 and oxidative stress, before and after oral glucose tolerance test (OGTT). Compared to placebo chocolate, dark chocolate ingestion improved FMD (P=0.03), wave reflections, endothelin-1 and 8-iso-$PGF_{2\alpha}$ (a marker of in vivo oxidative stress) (P<0.05). After placebo chocolate ingestion, FMD was reduced after OGTT from 7.88±0.68 to 6.07±0.76 (P=0.027), 6.74±0.51 (P=0.046) at 1 and 2 h after the glucose load, respectively. Similarly, after placebo chocolate but not after dark chocolate, wave reflections, blood pressure, and endothelin-1 and 8-iso-PGF(2α) increased after OGTT. Thus, we concluded that OGTT caused an acute, transient impairment of endothelial function and oxidative stress, which was attenuated by flavanol-rich dark chocolate. These results suggest cocoa flavanols may contribute to vascular health by reducing the postprandial impairment of arterial function and metabolism associated with the pathogenesis of atherosclerosis. Concordantly, we conducted further studies with black tea and demonstrated that it dose dependently increased FMD (from 7.8%, control, to 9.0, 9.1, 9.6 and 10.3% after each of the different flavonoid doses that we used, respectively, P = 0.0001). Of note, even only 100 mg/day (less than 1 cup of tea) increased FMD compared with control (P = 0.0113). FMD improvement after 800 mg/day was significant compared with control (P < 0.0001) but also to 100 mg/day (P = 0.0121) and 200 mg/day (P = 0.0275). Black tea intake also decreased office systolic (-2.6 mmHg, P = 0.0007) and diastolic (-2.2 mmHg, P = 0.006) blood pressure levels as well as the stiffness index (P = 0.0159), substantially without side effects. Thus, it is now the time to consider healthy foods as natural protective drugs and to promote the Mediterranean diet as a natural remedy against cardiovascular disease. Some small changes in the traditional Mediterranean diet should also be considered, introducing tea and small amount of cocoa as part of an healthy diet. Of note, healthy foods must not be promoted/considered as a sort of *alternative drugs* and then lead to decreased adherence to cardioprotective drugs.

Indeed, healthy foods must not be generally seen as an alternative choice but as the *wise companion* of healthy drugs.

Microbiota and cardiometabolic risk

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It is well established in traditional epidemiology that some chronic disease conditions tend to cluster in families, with an increased risk in first-degree relatives, but also an increased risk in second-degree relatives [1]. This fact is most often referred to as the heritability (heredity) of these diseases and explained by the influence of genetic factors, or shared environment, even if the more specific details or mechanism leading to disease are not known. In clinical medicine a positive family history is often asked for during consultations, but the information provided is sometimes not exact as unawareness, poor recollection of data or other factors bias the answers. Therefore new methods have to be explored in screening studies and register linkage studies to define and measure consequences of a positive family history of disease. Furthermore, recent studies have indicated that different genetic score of well-known genetic markers of disease conditions such as obesity, type 2 diabetes or myocardial infarction is only able to explain a minor proportion of this described heritability [2,3]. Thus, there is still a lack of knowledge to explain the so called *"missing heritability"* of these disorders [4]. One model for understanding this is that gene-environmental interactions and epigenetics will add information to explain the hereditability, besides influences of shared environment in a broader sense. This is still not a well-researched area which is why there is a need of more and better quality information from both populations and families on genetic profiling as well as on bodily function (phenotyping) and data on lifestyle and environmental exposures. Of special relevance is to elucidate on genetic and non-genetic mechanisms behind early cardiovascular and metabolic ageing [5], as a model for early disease onset within risk families. These associations are now being investigated in the ongoing Malmö Offspring Study (www.med.lu.se/mos), including genetic mapping as well as advanced phenotyping.

Of particular interest is to determine the role of **microbiome,** measured as **microbiota** (the gut bacteria composition and variety), and its association with dietary intake together with the genetic profile of the host, in relation to alterations in metabolism and immunological function [6]. This will be linked to other research areas in microbiology, nutritional sciences, technology and innovation for prevention. For example, functional food products can be developed and tailored to the match the profile and needs of the individual. Of special interest in a family perspective is that the microbiome of individuals is influenced in early life, first by the microbiota of the mother from exposure to the offspring during delivery and neonatal period [7]. Later on this is influenced by more or less shared microbiota patterns in the household during childhood and adolescence due to cohabitation. It is hypothesised that microbiota profile as well as dietary intake patterns may cluster within families. Recently it was discovered that there is also a specific serum biomarker, the pro-atherosclerotic metabolite, trimethylamine-N-oxide (TMAO) that is able to reflect the gut microbiome [8]. We will therefore, in pilot studies, measure this biomarker using plasma samples from existing biobanks within our consortium for evaluation of the TMAO marker status of individual microbiota. Interventions to change the microbiota have provided promising results [9,10] and been described as a potential treatment target for cardio-metabolic disease [11]. Such interventions should be based on the wider use of designed and tested functional food products as part of a healthy lifestyle in general.

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Serum uric acid and CV risk

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Cardiovascular diseases are the major cause of death in the Western world as a consequence of the elevated prevalence and poor control of cardiovascular risk factors in the general population. During the last 25 year many possible risk modifiable factors have been identified in addition to those included in the main CV risk algorhytms as elevated blood pressure, diabetes and lipid disorders. Elevated levels of serum uric acid are the mechanism responsible for the development of gout but have been also frequently associated with an increase in the individual risk of CV diseases in addition with the more consolidated CV risk factors. A recognition of an association among hyperuricemia, kidney diseases and cardiovascular diseases dates to the late 19th century, but has been recently resurged to investigation in reason of the increase in the amount of information about the possible pathogenetic mechanism(s) and the demonstration of a remarkable degree of residual cardiovascular risk in patients undergoing an approriate control of the many independent CV risk factors. The hypothesis linking uric acid with cardiovascular disease is well grounded in animal models where the development in hyperuricemia is associated with an increase in blood pressure that can be prevented by the use of xantine-oxidase inhibitors leading to a decrease in serum uric acid. Data from observational studies and physiological experiments suggest that there may be a causal relationship between plasma levels of uric acid and the incidence of cardiovascular and renal disease. However, definitely convincing evidence remains elusive for many different reasons that complicates the relationship between the study of uric acid, its determinants and its confounders. In particular among the confounders a prominent role is played by statistical and methodological issues as well as by the counfonding role of co-variates that might be also mediators of biological pathways (e.g kidney) or might variably interact with additional cardiovascular risk factors.

In particular the assessment of the role of uric acid as a risk factor for CV disease should be conducted in patients free from gout and kidney disease, with a balanced age-range and gender distribution and across a appropriate period of follow-up. Cross-sectional investigations that have been often claimed to confirm or deny the association between uric acid and CV disease are difficult to interpret because of the elevated number of co-morbidities that affect the subjects. However despite these limitations in the methodological approach, the possible association between uric acid and cardiovascular disease is well supported by several epidemiological observation, can be reasonably explained by a mechanicist approach and might be favorably modified by appropriate treatment strategies involving both a biochemical and a structural approach addressing the protection of target organ. Understanding the complex relationship between uric acid and cardiovascular diseases is necessary to quantify of uric acid as a risk factor and should force the researches and clinicians to balance evidence supporting causality vs. associations. From the epidemiological point of view the association between uric acid and subsequent cardiovascular disease remains uncertain. While some recent recent epidemiological studies have independently related uric acid to hypertension, diabetes, metabolic syndrome, renal disease and cardiovascular complications, other studies have found that, following adjustements for cardiovascular risk factors and estimated GFR the independent role of uric acid in cardiovascular disease cannot be confirmed.
As far as the mechanism responsible for the negative impact of uric acid on CV diseases, an remarkable involvement of the xantino-oxidase system has been proposed because of the huge oxidative stress that is associated with its activation. This would certainly imply the possibility of a twofold mechanism responsible for uric acid vascular damage with some important implications for the approteness of treatment.

All these evidence support a possible role of serum uric acid as an independent risk factor for cardiovascular disease and suggest the importance of a more extensive investigation with the aim to increase the possibility of effectively reduce the impressive burden of cardiovascular diseases.

Where are now and where are we going?
Pharmacotherapy of hypertension

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Appropriate management of patients with arterial hypertension represents one of the main objectives for cardiovascular disease prevention. Lifestyle changes may delay or even prevent hypertension in non-hypertensive subjects, delay or prevent pharmacological therapy in grade I hypertensive patients and contribute to BP reduction in hypertensive individuals already on medical therapy. Furthermore, lifestyle changes contribute to the control of other CV risk factors and clinical conditions. However, drug treatment is necessary in the majority of patients. The 2013 Hypertension Guidelines of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) reconfirm that diuretics, beta-blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers are all suitable for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in some combinations. However the choice of drugs should be individualized, taking into account the presence of associated risk factors, clinical conditions, and preclinical organ damage. Monotherapy can effectively reduce BP in only a limited number of hypertensive patients and most patients require the combination of at least two drugs to achieve BP control. The suggestion, given in the 2007 ESH/ESC Guidelines, of considering initiation with a drug combination in patients at high risk or with markedly high baseline BP is reconfirmed and reinforced by the 2013 Guidelines. An important practical issue is represented by the choice of the optimal combination of drugs. Guidelines indicate some combinations of drugs which should be preferred, due to the synergistic antihypertensive efficacy and the possible favorable reciprocal influence on side effects (figure).

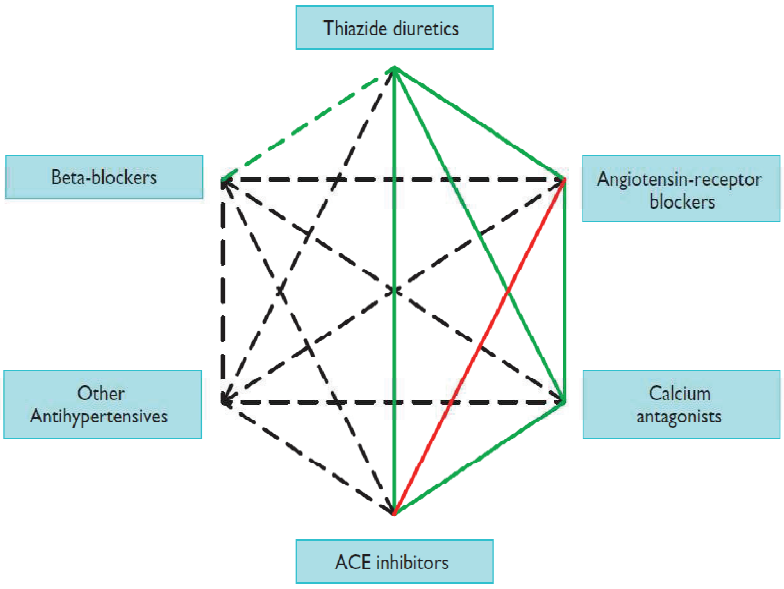

***Figure**: Possible combinations of classes of antihypertensive drugs. Green continuous lines: preferred combinations; green dashed line: useful combination (with some limitations); black dashed lines: possible but less well-tested combinations; red continuous line: not recommended combination.*

Trial evidence of outcome reduction has been obtained particularly for the combination of an ACE-inhibitor with diuretic, an angiotensin receptor antagonist and diuretic, a calcium antagonist and diuretic and an ACE-inhibitor with a calcium antagonist; the angiotensin receptor antagonist/calcium antagonist combination also appears to be rational and effective, and these combinations can thus be recommended for priority use. The combination of a beta blocker with a diuretic should be avoided in patients with metabolic syndrome or diabetes, with the exception of the new generation vasodilating beta blockers, that have a more favorable metabolic profile.

Appropriate choice of antihypertensive drugs may be crucial: very recently, adjusted drug treatment has been suggested to be superior to renal denervation for lowering blood pressure in patients with true resistant hypertension.

Guidelines also favor the use of combinations of two antihypertensive drugs at fixed doses in a single tablet, because reducing the number of pills to be taken daily improves adherence, which is unfortunately low in hypertension, and increases the rate of BP control. This approach is now facilitated by the availability of different fixed-dose combinations of the same two drugs, which minimizes one of its inconveniences, namely the inability to increase the dose of one drug independently of the other. This holds also for fixed-dose combinations of three drugs (usually a blocker of the RAS, a calcium antagonist and a diuretic), which are increasingly becoming available.

Among the new drugs for the treatment of hypertension aliskiren has been already approved for clinical use, and has proven to be effective in lowering blood pressure in younger and elderly patients; prolonged administration in combination treatment may exert favorable effects on asymptomatic organ damage, such as urinary protein excretion and on B-type natriuretic peptides, but no trial is available on the effect on cardiovascular morbid and fatal events in hypertension. Several other new drugs for the treatment of arterial hypertension are currently under investigation. Among them, angiotensin-receptor-neprilysin-inhibitors (ARNI) appear particularly promising. Very recently, in patients with heart failure and reduced systolic function, LCZ696 was significantly superior to enalapril in reducing the risks of death and of hospitalization for heart failure. Furthermore, this drug provides additive reduction of blood pressure as compared to valsartan with a good safety profile, as shown in a randomized trial in 1328 patients with mild-to-moderate hypertension, and therefore seems very promising also for the treatment of hypertensive patients. Other drugs, such as aldosterone-synthase inhibitors, dual vasopeptidase inhibitors, renin-prorenin blockers, aminopeptidase-A inhibitors, nitric oxide donors, AGE-breakers, AT2 receptor agonists, ACE-2 activators and rho kinase inhibitors may represent future options for the treatment of hypertensive patients.

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Pharmacotherapy of Coronary Artery Disease and Chronic Heart Failure

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Nowadays, coronary artery disease (CAD) as well chronic heart failure (CHF) are the main cause of mortality, morbidity and hospitalization worldwide. That is why it is very important to preformed an appropriate CAD and CHF prophylaxis and, if it necessary, to provide a treatment.
The main groups of drugs used in CAD and CHF pharmacotherapy are nearly the same. Patients with CAD should administered acetylsalicylic acid, ACE-I, β-blocker and statin. Chronic heart failure treatment also include ACE-I and β-blocker, which should be prescribed to every patient with left ventricular ejection fraction (EFLV) ≤40% with or without clinical symptoms. After that, when these fundamental treatment is not enough (NYHA II-IV and EFLV≤ 35%) the patient should additionally take mineralocorticosteroid antagonist (MRA) and/or diuretic. Pharmacotherapy with spironolactone or eplerenone lead to hospitalization and mortality reduction. On the other hand, diuretics have not been proved to diminished mortality or hospitalization incidence but they are preferred to be used in congestive, symptomatic patients to decrease CHF signs.
In both groups of patients ARB are treated as an alternative to ACE-I because of their negligible influence on morbidity and lack of mortality reduction especially in patients with stable CAD. Calcium channel antagonists should be rather avoided in patients with CAD and/or CHF however in some cases it is allowed to use amlodipine or felodipine. It is important that ivabradine was approved to be considered for use in patients with a contraindication to the β-blocker or β-blocker intolerance either in CAD and CHF treatment.

The role of statin, despite their benefit effects in CAD, is rather unconvinced in patients with CHF of ischemic and non-ischemic etiology.
It is very difficult to optimally treats patients with CAD and CHF, especially when they suffer from other cardio-vascular and non-cardio-vascular diseases e.g. diabetes, however the benefits from an appropriate pharmacotherapy for those patients mean life.

Natriuretic peptide-based therapeutic strategies

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Since their discovery in the early 80', natriuretic peptides (NPs) have been viewed as a potential therapeutic strategy in cardiovascular diseases, especially hypertension and heart failure. This approach, in fact, appears rational on the basis of the biological effects of NPs (natriuresis, vasorelaxation, sympathetic inhibition, renin and aldosterone inhibition, antifibrosis) as well as in view of both the early human applications and observational/epidemiological data. However, after the unsuccessful experience with direct infusion of NPs, which was associated with transient benefits, a more realistic approach, based on inhibition of enzymatic degradation of NPs and, thus, their accumulation in the blood, was experimented with some partial results. It turns out, indeed, that also the approach of inhibiting Neutro-endopeptidases, (NEP) was not successful, probably in view of the concomitant accumulation of other peptides, such as angiotensin II and was abandoned. At the same time, the attempt to develop a compound, which was able to inhibit both NEP and ACE (omapatrilat, vasopeptidase) was interrupted after the clinical experience of serious angioedema especially in black people. (1-2)
More recently, the development of a compound containing both an angiotensin receptor blocker (ARB - valsartan) and a neprilysin (NEP) inhibitor has turned out to represent a plausible approach in cardiovascular disease .
The prototype of this new class, defined ARNI (angiotensin receptor-neprilysin-inhibitor), LCZ696 has been first tested on intermediate endpoints in hypertension and heart failure (Paramount Study) showing consistent reductions of blood pressure compared to valsartan alone(3) and heart failure biomarkers (4).
Most recently, in the PARADIGM-HF trial, LCZ696 has shown a 20% highly significant reduction of the primary composite endpoint of cardiovascular (CV) death and hospitalizations, as well as of CV death (-20%) and overall mortality (-16%) compared to enalapril

(20mg/day) in a very large population of patients with heart failure, NYHA class II-IV, and ejection fraction ≤35%. These exciting new data are associated with a good tolerability and safety profile (5).
More studies are on the way to further define the clinical characterization of this new NP-based therapy in CV disease.

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Polypill Concept Revisted

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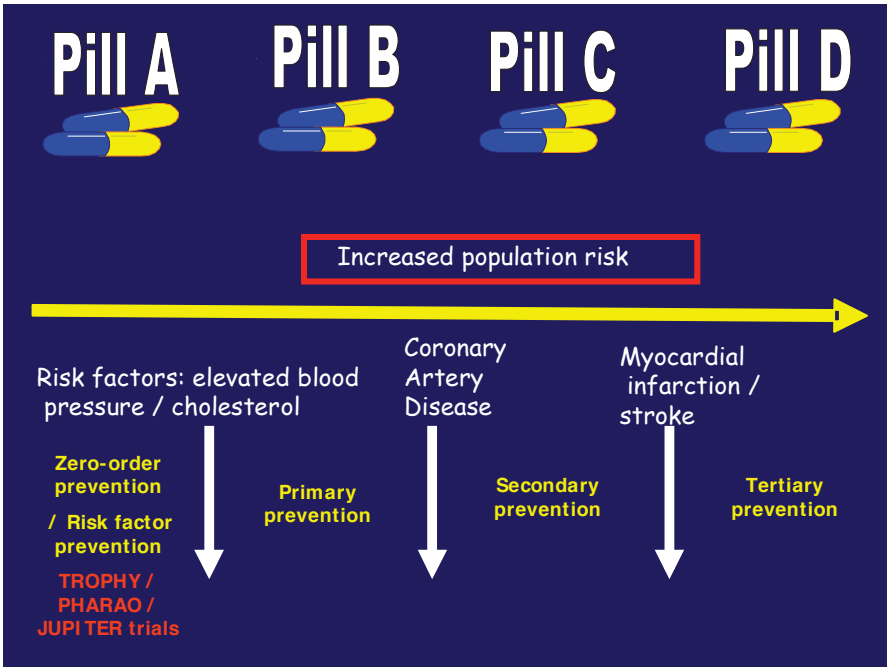
A polypill by common definition, is a medication that is a drug product in pill form (tablet or capsule) that combines multiple active pharmaceutical ingredients. An occasional synonym is "combopill" or "polycap". It is commonly manufactured as a fixed-dose combination (FDC) drug product targeting treatment or prevention of chronic disease. FDC, on the other hand, which is a formulation including two or more active pharmaceutical ingredients combined in a single dosage form is manufactured and distributed in certain respective fixed doses. Polypills may be aimed to be consumed by healthy people as a means of preventive medicine (aspirin and statin polypills in certain populations), and/or treating actual pathophysiological condition (aspirin / statin/ antihypertensive or two-three antihypertensives). Polypills reduce the number of tablets or capsules (generally orally administered) that need to be taken and they increase patients' compliance. The term polypill was first used in the context of cardiovascular disease prevention. We could postulate different polypill concepts as shown on the drawing below (Filipiak, 2012).



Polypill A could be suggested for in prehypertension, in subjects with family cardiovascular history, inflammation indicated with C-reactive protein elevation (JUPITER study inclusion criteria) and should include statin and aspirin or low-dose ACE-inhibitor. Polypill B could be a drug consisting of aspirin, statin and two antihypertensives, Polypill C should have also beta-blocker, potentially with vasodilatory activities (carvedilol, nebivolol), Polypill D should also have at least two antiplatelets (aspirin and clopidogrel or aspirin and ticagrelor).
Two trials completed in polypill area were TIPS and UMPIRE.
Both included over 4000 patients. Nowadays several clinical trials ongoing test the hypothesis of polypill.
From those trials, the biggest are: FOCUS trial (polypill: aspirin/simvastatin/ramipril), HOPE-3 trial (testing in one trial group: rosuvastatin/candesartan/hydrochlorothiazide), TIPS-3 trial (testing polypill: hydrochlorothiazide/atenolol/ramipril/simvastatin), Poly Iran trial (testing polypill: aspirin/enalapril or valsartan/atorvastatin/hydrochlorothiazide), and HOPE-4 trial (testing

three different polypill combinations with aspirin/simvastatin/atenolol/ramipril/hydrochlorothiazide).

Out of those trials, the biggest are: HOPE-3 with 12 705 patients (results expected in 2016), HOPE-4 with 9 500 patients (results expected in 2017 or 2018), Poly Iran with 7 000 participants (results expected in 2018 or 2019). The era of polypill trials is coming.

A Global Summit on Combination Polypharmacy for cardiovascular diseases was held on September 25–26, 2012 in Canada. The conclusions of this Summit will be presented also in the lecture, which underline the necessity of regulatory guidelines updated and clarification, the necessity of four or five-drug combinations to be approved. The Summit also noted the need for further research funding to support trials testing effects of the combination pill on clinical outcomes in specific patient groups and to test expansion of the concept to other patient groups who are at high risk for cardiovascular diseases such as those with diabetes or HIV/AIDS.

The polypill concept must be revised and nowadays it deals not only with hypertension but with general prevention of cardiovascular diseases.

Drug adherence: a major challenge in cardiovascular protection

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The treatment of essential hypertension is based essentially on non-pharmacological recommendations and on the prescription. Because of the silent nature of hypertension long-term adherence to therapy is one of the major issues of the management of hypertensive therapy. Indeed, it is well recognized that many patients interrupt completely their antihypertensive treatment after one year and this lack of persistence has a major impact on our ability to control blood pressure in the population. Today, there are multiple ways of assessing drug adherence in patients but only very few of them are accurate and the most accurate ones are difficult to implement in clinical practice. Thus, physicians have no real capacity to establish a correct diagnosis of non persistence or poor adherence even in high risk patients such as patients with resistant hypertension. Therefore, there is an urgent need to develop new techniques or devices to help physicians in their ability to handle adherence to therapy and to improve blood pressure control in the population.

Physician (Investigator) Inertia in Apparent Treatment Resistant Hypertension - Insights From Large Randomized Clinical Trials

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Background. Treatment of resistant hypertension has attained much attention during the past few years and naturally so has the prevalence of resistant hypertension. In the search for sources of such documentation the lack of blood pressure (BP) control in randomized clinical outcome trials in hypertension has been used as indication of treatment resistant hypertension. In the present study we aimed at using previously unpublished information from monitoring of clinical trials in investigating the mechanism explaining why large fractions of patients in the trials remained uncontrolled for their high BP.
Methods. We report insight information from LIFE (n=9,193), VALUE (n=15,245), ASCOT (n=19,257) and ACCOMPLISH (n=11,506). Data stored during the course of the trials for monitoring purposes were scrutinized for fractions of patients with BP control, which was BP <140/90 mmHg in all trials, and we identified monitoring data showing fractions of patients who had been titrated up to the various dosing levels or combinations of study drugs in the trials. Fractions of patients who had not been titrated up on drugs and who remained without BP control identified the level of physician (investigator) inertia in these trials.
Results. In the LIFE Study the majority of patients remained with systolic BP >140 mmHg throughout. Approximately 1500 patients remained on the first dose titration step despite not having reached target BP. In the VALUE Trial 59.5% had reached systolic BP target 2 years into the study; 23.9% of patients remained on lowest study dose and only 15.1% had been titrated up to highest study dose. In the ASCOT Trial as many as 28% of participants had not reached target diastolic BP at year 4 in the study, and of these patients 37% still remained on the first drug dose titration step.
In the ACCOMPLISH Trial approximately 80% had achieved the systolic BP target at study end; however, during the course of the trial approximately 25% of participants remained uncontrolled and at 6

months almost 60% of these patients had not been titrated to highest drug dose level.

Conclusion. These data, taken from the monitoring phases of large outcome trials in hypertension, show that inertia, the lack of titration of study drugs to higher dosing levels or drug combinations according to the study protocols, is a major cause of not reaching BP targets in the trials. Thus, fractions of patients not reaching BP targets in outcome trials cannot be taken as evidence of treatment resistant hypertension.

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Implementation of the guidelines

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Current practice of medicine is based on sets of recommendations using data from clinical trials and endorsed by scientific societies on local as well as international level. Clinical trial – guideline – education process has profound effect on cardiology research and practice however, transferring guidelines from paper into practice has proven to be frustrating and may underlie the low efficacy of both primary and secondary cardiovascular prevention in many regions.

There are three major barriers to following practice guidelines: knowledge, attitude and behavior. Knowledge barrier is related to the volume of information, proliferation of guidelines and frequent updates. Practice demands and reimbursement may also influence priorities of a physician, placing some activities (i.e. blood pressure control) at a lower level. However, the physician's knowledge of guidelines does not itself lead to better guideline implementation.

Attitudes may refer to lack of acceptance of some recommendations or guidelines applicability to certain populations. Credibility may be also questioned based on disparities between different sets of guidelines and lack of uniform statements by different group of experts. For some practitioners, an important barriers is the feeling of inability to modify patient life style, lack of motivation and difficulties to adopt new routines.

Behavior barriers are related to certain inherent limitations of guidelines themselves which do not address many questions important for clinical practice due to insufficient evidence from clinical trials. Ambiguity and inconsistency may cause different physicians to take different actions for the same group of patients. For the best quality of guidelines the appropriate instruments for their construction and evaluation has been created (Appraisal Of Guidelines For Research and Evaluation).

Despite the significance of wide implementation of current clinical knowledge into daily practice there is little research on the effect of different implementation strategies. Team-based care seems to offer better control of cardiovascular risk factors as was shown by the results of EUROACTION and Canadian Hypertension Education Program. Also, trials like STITCH-care (Simplified Treatment Intervention to Control Hypertension) demonstrated that guideline simplicity promotes their implementation. However, new studies seeking a better strategies for cardiovascular guideline implementation in different clinical settings are needed.

Predictors of Hypertension Onset in Children

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High blood pressure is a clearly established, but modifiable, risk factor for early disability and death. While few would dispute the importance of taking effective steps to identify and manage this condition in middle-aged and elderly people, relatively little attention has been paid to the problem of high blood pressure in children. It is now established, however, that high blood pressure is detectable in children and adolescents, is surprisingly common, and is increasing in prevalence. Over the last several years hypertension in children and adolescents has gained ground in cardiovascular medicine, thanks to the progress made in several areas of pathophysiological and clinical research. After the agreement to define reference values it is interesting to know the factors related to the risk to develop primary hypertension. Today it is accepted that blood pressure phenotype is the result of the interaction among genetic, environmental and fetal factors. Family history of hypertension, the presence of overweight or obesity, and salt consumption are factors traditionally associated with high blood pressure. The importance of intrauterine and early life events in the development of so-called non-communicable disorders has been emphasized, contributing to the developmental origins of cardiometabolic disease mainly in adults. The phenotypic induction, subtle changes that occur in critical periods of life but have long-ranging effects, leads to changes in the individual programming origins of health or disease.

Clinicians should develop a consistent approach to blood pressure measurement and factors related to developing high blood pressure as part of our everyday management of young patients.

Hypertensive heart disease

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In hypertension, left ventricular hypertrophy is initially a compensatory process, that represents an adaptation to increased ventricular wall stress; however, it is also the first step toward the development of overt clinical disease. The presence of LVH predisposes to the development of myocardial ischaemia and heart failure, but is also associated with a higher incidence of stroke. The incidence of CV events in hypertensive patients is clearly related to the modifications of cardiac hypertrophy during treatment, and the LVH regression is associated with a better CV prognosis, even independently from the modification of other risk factors, especially BP levels. In some cases, however, it is difficult to obtain LVH regression. It is probably not the quality but the quantity of LV mass that should be assessed (i.e. the collagen content, contractile molecules).

For this reason most guidelines recommend the assessment of cardiac target organ damage in hypertensive patients for risk stratification at baseline. The decrease or the normalization in LV mass and other cardiac structural and functional abnormalities may be associated with a significant reduction of the incidence of CV events, providing evidence that pharmacological intervention is effective, additional to the measurements of clinic, central aortic and 24 hors blood pressure measurement. For this reason it appears reasonable to search for changes in anatomic and functional aspects of hypertensive heart disease, not only for the initial stratification of CV risk, but also during follow-up.

Several methods are currently available for the assessment of LVH;the techniques differ in cost, availability, sensitivity and specificity. Electrocardiography should be part of all routine assessment of subjects with high blood pressure; however, despite its good specificity, the sensitivity for LVH detection is low.

Echocardiography represents a valuable method for the detection of LVH in hypertensive patients, due to its wide availability and its relatively low cost, with the main limitations of a lower spatial resolution and reproducibility in comparison to MRI.

Target organ damage: clinical implications of recent findings. Large vessels

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For a long time, hypertension Guidelines focused on blood pressure values as the main variables determining the need and the type of treatment. Since 2003 the ESH-ESC Guidelines underlined that diagnosis and management of hypertension should be related to quantification of global cardiovascular (CV) risk, and the subsequent ESH ESC Guidelines have further emphasized the importance of assessing the presence of subclinical target organ damage (OD) for total CV risk assessment. In fact, an extensive evaluation of OD may increase the number of patients classified at high CV risk and therefore strongly influence the clinical management of patients. Measurement of intima media thickness and plaques and/or of arterial stiffness are the most frequently used forms of OD, but also several other approaches have been proposed and might gain importance in the next future (table).

Marker	Cardiovascular predictive value	Availability	Reproducibility	Cost-effectiveness
Electrocardiography	+++	++++	++++	++++
Echocardiography, plus Doppler	++++	+++	+++	+++
Estimated glomerular filtration rate	+++	++++	++++	++++
Microalbuminuria	+++	++++	++	++++
Carotid intima–media thickness and plaque	+++	+++	+++	+++
Arterial stiffness (pulse wave velocity)	+++	++	+++	+++
Ankle–brachial index	+++	+++	+++	+++
Fundoscopy	+++	++++	++	+++
Additional measurements				
Coronary calcium score	++	+	+++	+
Endothelial dysfunction	++	+	+	+
Cerebral lacunae/white matter lesions	++	+	+++	+
Cardiac magnetic resonance	++	+	+++	++

Several studies have demonstrated and confirmed the important prognostic significance of intima-media thickness, as measured by ultrasound. Current Guidelines recommend a cut off value of > 0.9 as a marker of OD, but it should be kept in mind that the increase in risk associated with IMT is continuous: a large meta-analysis of data collected in 8 studies in general populations, including 37,197 subjects who were followed up for a mean of 5.5 years, has demonstrated that for an absolute carotid IMT difference of 0.1 mm, the future risk of

myocardial infarction increases by 10% to 15%, and the stroke risk increases by 13% to 18%. Some studies have suggested that that the net risk reclassification provided by assessment of IMT on the common carotid artery might be limited, while the assessment of IMT at the level of the carotid bifurcation and of the internal carotid artery as well as the detection of plaques may significantly increase the ability to identify patients at high risk of CV events in the future. Also measurement of arterial stiffness for CV risk quantification has gained increasing importance in the last years. Large artery functional damage can be assessed non-invasively through the measurement of arterial stiffness, central BP, and central augmentation index (AIx). During the last years the research in this field has made available a large amount of data on the association between various measures of arterial stiffness and the occurrence of CV events. The largest amount of evidence available for aortic stiffness, measured through carotid-femoral PWV, which is currently considered the most simple, non-invasive and robust measure of arterial stiffness for clinical use. Other approaches, such as the analysis of pulse wave contour, recorded by applanation tonometry or measurement of local stiffness through high resolution radiofrequency-based techniques, are widely used as research tools and could gain also clinical relevance importance in the near future, in view of the accumulating amount of scientific data.

At present it has not been demonstrated whether a decrease of IMT progression is associated with a reduction of cardiovascular events and an improvement in prognosis; the independent prognostic significance of changes over time of indices of arterial stiffness has been demonstrated in patients at high CV risk but requires further confirmation. In conclusion assessment of vascular organ damage represents a valuable tool for a better assessment of global CV risk and for the optimal management of hypertensive patients.

Small Vessels

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The presence of structural alterations in the small resistance vessels microcirculation may be considered an important link between hypertension and ischemic heart disease, heart failure, cerebral ischemic attacks and renal failure. It is now widely accepted that structural abnormalities of resistance vessels are common alterations associated with chronic hypertension. An increased arterial wall thickness together with a reduced lumen may play an important role in the increase of vascular resistance, and may also be an adaptive response to the increased haemodynamic load. In the last years, many experimental studies have indicated that changes of small artery structure in hypertension are the consequence of either eutrophic or hypertrophic remodeling (re-arrangement of the same amount of wall material around a narrowed lumen or smooth muscle cell hypertrophy/hyperplasia, respectively). The increased media to lumen ratio was demonstrated to be a powerful predictor of cardiovascular events in a high risk population of patients with primary and secondary hypertension. The prognostic importance of structural alterations of subcutaneous mall resistance arteries was extended to patients with essential hypertension at low-moderate cardiovascular risk, and to major cardiovascular events (myocardial infarction, stroke and sudden death). The possible regression of vascular alterations is an appealing goal of antihypertensive treatment. A complete normalization of small resistance artery structure was demonstrated in hypertensive patients, after prolonged and effective therapy with dihydropyridine calcium channel blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. No effect was observed with beta-blockers and diuretics despite similar blood pressure reduction. Recent data suggest also the presence of a prognostic relevance of the extent of the regression of vascular structural alterations. However, prospective studies, possibly with less-invasive approaches, are needed in order to clarify whether structural alterations in small resistance arteries may be definitely considered a surrogate endpoint in the evaluation of the effects of

antihypertensive treatment. Recently, a non invasive evaluation of retinal arteriolar morphology by Scanning Laser Doppler Flowmetry was proposed. The information provided seems to be similar to those obtained with invasive assessments, thus opening interesting clinical perspectives in terms of risk stratification in hypertensive patients.

Brain damage in relation to high blood pressure

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Cerebrovascular disease is a major cause of death and disability with high blood pressure being its most potent of currently known modifiable risk factors. Subclinical injury in the brain is one of the earliest systemic markers of hypertension. However, its pathophysiology is not fully understood.
Although age and high blood pressure (BP) are traditionally considered the main risk factors for both silent and overt cerebral vascular injury, there are emerging new BP-derived factors in the pathogenesis of brain damage. There is growing evidence that central systolic BP values is more closely associated with cerebral white matter lesions (WML) than brachial systolic BP. Indeed, central BP, contrary to the brachial BP, is the true driving power for central organ supply, including brain. Furthermore, BP variability has recently been shown to be associated with both development and progression of cerebral WML and cerebral microbleeds (CMB). BP fluctuations are suggested to be caused by a complex interaction between external environmental stimuli and the response of cardiovascular control mechanisms.
Arterial stiffness might be a crucial factor underlying the relationship between central BP, as well as BP variability and cerebral damage by disproportionate increase of aortic BP and reduced dampening of BP changes in response to changes in stroke volume, respectively. Subsequent pulsatile flows transferred into the tissue may explain cerebral injury such as WML and CMB and the increased incidence of stroke and dementia.
In conclusion, there is growing evidence on prognostic role of new BP indices beyond that conferred by maximum and minimum peripheral values for hypertensive central organ damage.

The demonstration that both central BP and BP variability carry independent prognostic information for brain damage has the potential of modifying our current understanding of the importance of BP panel that finally could have clinical relevance.

Diabetes: focus on glycaemic control

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Diabetes mellitus is one of the most common chronic diseases worldwide. The prevalence of both major forms of diabetes, type 1 and type 2, is rapidly increasing. It has a large impact on the patients' life expectancy, mainly due to its complications, and it constitutes a huge challenge for the health systems. According to the estimations of the World Health Organization the number diabetes mellitus cases worldwide will reach almost 500 millions by the year 2030.
The major cause of excessive mortality, particularly among type 2 diabetes patients, is diabetic macroagniopathy. There have been a number of clinical trials performed to investigate possible preventive measures in order to reduce cardiovascular events and related mortality among patients with diabetes. Several large randomized clinical trials, such as UKPDS, ACCORD, ADVANCE, VADT, examined whether in type 2 diabetes subjects with poor metabolic control the intensive glycemic treatment as compared to the standard care reduces the risk of cardiovascular events and is safe. Little evidence was shown to support a hypothesis that intensive hypoglycemic therapy in subjects with long diabetes duration may improve vascular prognosis. These studies substantially influenced clinical guidelines and clinical practise as their results showed that glycemic goals should be individualized in patients with type 2 diabetes. Several other recent trials investigated, with variable results, efficacy of other approaches, such as Mediterranean diet, physical exercise or new pharmaceutical hypoglycaemic interventions (DPP-4 inhibitors). Future studies will show whether new classes of glucose lowering medications, GLP1 agonists and SGLT2 inhibitors, with interesting clinical properties, such as promotion of weight reduction and low risk of hypoglycemia, will improve cardiovascular prognosis in patients with type 2 diabetes.

The Ederly

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A high percentage of patients in the Europe and the United States have hypertension that is uncontrolled. Most of these belong to the most rapidly growing demographic group i.e., the elderly. It is estimated that more than 70% of medical practice will be directed to geriatric needs in the coming years. Compared with younger patients with similar blood pressure, elderly hypertensive patients have lower cardiac output, higher peripheral resistance, wider pulse pressure, lower intravascular volume, and lower renal blood flow. These age-related pathophysiologic differences must be considered when treating a hypertension in the elderly. Data from randomized controlled trials suggest that treating hypertension in the elderly, including octogenarians, may substantially reduce the risk of cardiovascular disease and death. The consensus, therefore, is that it is appropriate, even imperative, to treat elderly hypertensive patients. However, treatment remains challenging because of comorbidities and aging-related changes which tremendously affect the management of their hypertension. The average 75 year old elderly subject is on more than six medications and some of these are for high blood pressure, but others interact with antihypertensive drugs, and some, directly affect blood pressure. In the process, these frail patients are exposed to a host of drug-related adverse effects. Thus, it is relevant to question the net benefit of treatment in this age group as the race for more effective control of hypertension and its associated complications in the elderly is far from won.

Resistant hypertension - prevalence and clinical characteristics

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Resistant hypertension (RHTN) is defined as office blood pressure that remains above goal despite the concurrent use of 3 antihypertensive agents, in optimal doses, one of them being a diuretic. Recent studies indicate that RHTN is present in about 10-12% of the treated hypertensive population.
It has been shown that RHTN as compared with more easily controlled HTN is associated with more pronounced cardiovascular risk factors profile and worse prognosis. In general, management of resistant hypertension adopts a 2-step approach: first, confirmation of true resistance [by simultaneous recognition and correction of factors related to pseudo-resistance] and second - identification of the factors that contribute to treatment resistance in a given patient.
The large, prospective systematic studies showed that patients with true RHTN have very high prevalences of obstructive sleep apnoea [OSA] ranging from 66% to 82% and metabolic syndrome [MS], also frequently coexisting with each other. Recent studies also indicate, that RHTN is often associated with secondary forms of hypertension, particularly with primary hiperaldosteronism [PA] and renal artery stenosis [RAS] .
This may suggest a common pathological phenotype related to RHTN, or a common etiologic substrate. The available data suggest that evaluating and treating RHTN according to these clinical characteristics and comorbidities, may contribute importantly not only to blood pressure control, but also to improving overall cardiovascular outcomes in this patient population.

Observational studies have enabled identification of those demographic and lifestyle characteristics associated with RHTN, and the role of secondary causes of HTN is well documented (4). It should be noted that available studies are limited by the high cardiovascular risk and the presence of multiple co-morbid disease processes -

including older age, diabetes, and chronic kidney disease - which confound interpretation of the results.
However, patients with true RHTN have not been widely studied, particularly with regard to the systematic evaluation of those factors which are either associated with or which may promote resistance to antihypertensive treatment. Therefore the aim of our study was to identify the clinical characteristics of patients with true RHTN and to evaluate the prevalence of factors known to contribute to treatment resistance – including obstructive sleep apnea (OSA), metabolic syndrome (MS) and secondary causes of HTN – and their relationship to BP profiles and the presence of target organ.

Resistant hypertension is defined as failure to achieve goal blood pressure (BP) when a patient adheres to the adequate doses of 3 antihypertensive drugs including a diuretic. Although the definition of resistant hypertension is arbitrary relative to the number of antihypertensive medications required, the concept of resistant hypertension is focused on identifying patients who are at high risk of having reversible causes of hypertension and/or patients who, because of persistently high BP levels, may benefit from special diagnostic or therapeutic considerations.

Renal Denervation: Caution is still required

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Despite the availability of multiple classes of orally active antihypertensive treatments, resistant hypertension (RH) remains an important public health issue in 2014. The failure of purely pharmacological approaches to treat RH has stimulated interest in invasive device-based treatments. Catheter systems using radiofrequency (RF) energy or ultrasounds have been developed, allowing a percutaneous endovascular approach to renal denervation and providing patients with RH with a new therapeutic option. Initially, this technique was evaluated only in open-label trials including small numbers of highly selected patients with resistant hypertension and suitable renal artery anatomy. The first two studies of renal denervation with a RF catheter, Symplicity HTN-1 and 2, reported 25–30 mmHg decreases in office systolic blood pressure (BP) at 6 months in patients with RH, with less than 5% of patients having procedural adverse events. Following these results, the procedure was made available in Europe despite uncertainty about both safety and efficacy related to the limitations of most previous studies potentially jeopardizing their internal validity (open-label design subject to expectation, performance and evaluation biases and to Hawthorne effect, and lack of standardization of BP measurements and of antihypertensive treatment). Indeed, the prospective, blinded, randomized, sham-controlled trial Symplicity HTN-3 (RF Medtronic® system) failed to meet its primary and secondary efficacy endpoints reporting much smaller and non significant difference in the changes in both office BP (-2.39 mmHg [95%CI, -6.89 to 2.12], p=0.26) and ambulatory BP -2.0 mmHg (95% CI, -5.0 to 1.1, p=0.98) between the renal denervation and the control group than in previous studies. The per procedural adverse event rate was low and there were no significant differences in safety between the two groups.

The magnitude of BP response has been linked to baseline BP, operator experience, and the procedural performance, but there is no marker of procedural success. These findings raise the possibility that previous trials attributed the BP response to a treatment effect of renal denervation, when the effect may have been due to a large placebo response, the Hawthorne effect, regression to the mean, measurement bias, unknown co-interventions, or unintended bias. However, this study also suggests that a subset of patients may be considered as responder. Ethnicity, age, and renal function were among the contributing factors associated with the BP response to renal denervation in Symplicity HTN-3. There may be variable involvement of prevailing renal sympathetic nerve activity and neural mechanisms to the pathophysiology of RH which may also contribute to the variable BP response, although there is no simple and reproducible way to assess this prior to renal denervation. The results of the Symplicity HTN-3 study are not directly applicable to other clinical settings or other renal denervation catheters that may achieve different degrees of renal nerve ablation and have a different safety profile. Properly designed studies of sufficient duration remain necessary to evaluate the efficacy and safety of each of these catheters in a well-defined population of patients and to identify simple, reproducible, and accurate preoperative predictors of the BP response to renal denervation. The long-term risk of progression preexisting renal artery stenosis or de novo renal artery stenosis is probably low but remains also to be properly evaluated. The best way to ensure the rigorous follow-up of patients after renal denervation remain to include them in clinical trials or international registries. Tertiary hypertension clinics or ESH Hypertension excellence centers should be preferred to perform extensive workup and treatment adaptations for RH and take the decision for renal denervation.

Baroreflex stimulation and other methods of interventional management

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There is growing interest in interventional management of resistant hypertension. While most of the studies focused on renal denervation (RDN), several other novel methods may play an important role in treatment of drug-resistant hypertension.

Carotid sinus baroreceptor stimulation is based on solid scientific background linking baroreflex mechanisms to short-term and long-term cardiovascular regulation. The blood pressure lowering efficacy of device-based chronic electric baroreceptor activation therapy has been demonstrated in high cardiovascular risk patients with resistant hypertension. The procedure-related complication rate with the first generation device was 20-30%. This risk is much smaller with the second generation systems. Apart from peripheral blood pressure, baroreflex activation therapy reduces central blood pressure, augmentation index and pulse wave velocity, and has been shown to reduce left ventricle hyperterophy. This treatment option is now approved in Europe for the treatment of severe resistant hypertension.

Arteriovenous anastomosis using the ROX Coupler device provides a novel approach in the management of patients with drug resistance. First studies in humans have demonstrated reduction in both office and ambulatory blood pressures. Potential therapeutic effect of the anastomosis device may be related to reduction total systemic vascular resistance and an increase in cardiac volumes and reduction in afterload, resulting in an overall reduction in cardiac work despite increased cardiac output.

Deep brain stimulation (DBS) has gained significant recognition after entering a clinical practise for the treatment of Parkinson's disease. More recently, significant blood pressure reduction with the use of brain stimulation of the ventrolateral periadeuquotal gray/periventricular gray matter has been demonstrated in two patients with resistant hypertension.

Whether DBS may be offered widely as a therapeutic tool to reduce blood pressure and improve cardiovascular outcomes in patients with resistant hypertension clearly merits further investigation.

Much recent attention has been given to the carotid body because of its potential role in cardiovascular disease states. Carotid body acquires tonicity in hypertension. Carotid body modulation may be a powerful way to temper excessive sympathetic discharge in resistant hypertension. Studies in spontaneously hypertensive rats demonstrated that carotid sinus nerve denervation resulted in a parallel reduction in BP and sympathetic activity. Moreover, when combining RDN with carotid body denervation, the decrease in blood pressure is even more pronounced resulting in an additive response to the both procedures. These findings support the concept that two independent mechanisms, renal sympathetic activation and tonic sympathetic activation of the arterial chemoreceptors are critically involved in human hypertension. Carotid body denervation is currently being investigated in patients with resistant hypertension (NCT01729988 at http://www.clinicaltrials.gov/).

Blood Pressure Variability

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This presentation will address several aspects of the blood pressure (BP) variability phenomenon. One, the mechanisms so far discovered that are responsible for the marked BP variabilities that occur over the 24 hours. Two, the changes of 24 h BP variability with aging, hypertension and antihypertensive treatment. Three, the evidence that 24h BP variability shows a relationship with asymptomatic organ damage and can independently predict the incidence and risk of cardiovascular morbid and fatal events. Four, the formidable limitations faced by studies on 24h BP variability when non-invasive ambulatory BP monitoring is used, given that this approach only provides a microscopic fraction of the BP values (~ 100.000) taking place throughout the day and night, thus offering only a pale imagine of this phenomenon. Because of this, major advancements in this area will be to develop 1) beat-to-beat non-invasive BP measurements that can be employed in ambulant patients and 2) make the devices so inexpensive and simple that their use can be extended to a large number of individuals, thereby allowing longitudinal prognostic studies.

Finally, a review will be made of the evidence available on the mechanisms and clinical significance of long-term BP variability, i.e. BP variability between days and seasons as well as between visits during antihypertensive therapy.

It will mentioned that visit-to-visit BP variability is likely to have prognostic significance but that gaps in knowledge and technical limitations exist, so that the results need to be interpreted with a degree of caution.

H_2S donors and sulphydrylated ACE inhibitors and their role in cardiovascular diseases

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Hydrogen sulfide (H_2S) is a gaseous mediator strongly involved in the cardiovascular homeostasis that has vasorelaxant properties. It is generated within the endothelium wall mainly by cystathionine-γ-lyase (CSE) that converts L-cysteine, the substrate, in hydrogen sulfide.
We have recently demonstrated that CSE/L-cysteine/ H_2S pathway, and its interplay with eNOS/L-Arg/NO pathway, regulates vascular tone. Indeed, we have identified phosphodiesterases inhibition as one of the molecular event responsible for H2S action, and by using knock-out mice for PKG and CSE, we confirmed the role of cGMP in vascular responses to H_2S.
Following this issue, we have attempted to assess the role of H_2S in systemic blood pressure control. In particular, we have tested the possibility that H_2S could account for some of the extra beneficial effect of sulphydrylated ACE inhibitors. Indeed, we have shown, by using an animal model of hypertension (SHR) where H_2S biosynthesis is impaired, that only sulphydrylated ACE inhibitors treatment rescued the vascular response in terms of blood pressure and vascular reactivity.
Our data establish that sulphydrylated ACE inhibitors modulates vascular function through rescue operated by H_2S pathway in SHR model, suggesting a peculiar mechanism disjointed by ACE inhibition and based on H_2S release, which maybe explicative of beneficial effects of sulfhydrylated ACE inhibitors reported in literature.

Novel targets in cardiovascular protection – Inflammation

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While the role of inflammation in cardiovascular risk is relatively well defined, therapeutic targeting of inflammation has not been so far introduced into clinical practice. This is in part related to the lack of specific biomarkers of inflammation in CVD, as CRP and hsCRP value is being disputed. Several clinical trials are now on the way to address the possible role of cytokines such as IL-1, IL-6 or TNF-alpha as targets for future anti-inflammatory therapies in patients with very high cardiovascular risk. Number of traditional risk factors for atherosclerosis is known to modulate inflammation in CVD such as obesity, hypertension, hypercholesterolemia, diabetes mellitus. Importantly recent data suggest that immune dysregulation is part of the pathogenesis of all of these risk factors. Therefore targeting inflammation in CVD may help to modulate these risk factors.
The major dispute currently is related to sites of inflammation that affect cardiovascular risk. While immune activation may occur in the vasculature itself, distant sites of infection and inflammation are known to significantly affect cardiovascular risk. These include disease states such as exacerbations of COPD or periodontitis. Recent meta-analysis shows a clear link between periodontitis and atherosclerosis/cardiovascular risk, independently of traditional risk factors. We have made similar observations in respect to hypertension. Moreover intensive treatment of periodontitis exerts vasoprotective effects. Can we assume that removal of sources of systemic immune activation could be more effective in alleviating cardiovascular risk than targeting individual cytokines? Finally, regular physical exercise which is known to be particularly effective in cardiovascular prevention through its direct effects on endothelial function, also has

important immunomodulatory effects which could be additionally utilized in targeting inflammation.

In summary, there are numerous strategies aiming on targeting inflammation in cardiovascular disease. These include direct inhibition of the effectors of the immune system, or simple procedures preventing the development of systemic inflammation. It is therefore critical to develop biomarkers that would allow us to stratify cardiovascular risk patients depending on their needs for the vast range of anti-inflammatory treatments available.

Arterial Stiffness as Novel Target in Cardiovascular Protection

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A major reason for measuring arterial stiffness in clinical practice in hypertensive patients comes from the demonstration that arterial stiffness has predictive value for CV events. An increasing number of methods have been developed for measuring arterial stiffness. The Gold standard is the measurement of carotid-femoral pulse wave velocity. Whether the reduction in arterial stiffness translates into a reduction in CV events (ie whether arterial stiffness is a surrogate end-point) has not yet been demonstrated. However there is reasonable evidence for targeting the reduction of arterial stiffness during treatments used for CV protection. Antihypertensive treatments can reduce arterial stiffness "passively" through the reduction of blood pressure (BP) that unloads the stiff components of the arterial wall. However, observational studies have reported that long-term antihypertensive treatment is able to lower arterial stiffness beyond BP reduction. This BP-independent destiffening effect occurs likely through long term arterial remodeling, reduction in collagen density and microinflammation, and rearrangement of the wall materials. Thus, a sustained fall in BP is mandatory in hypertensive patients to lower arterial stiffness through long-term arterial remodeling. More specifically, destiffening drugs should target specific molecular components of the arterial wall, namely those involved in fibrosis. Blockers of the renin-angiotensin aldosterone system (RAAS) are privileged antihypertensive drugs for such a BP-independent effect on arterial stiffness.
In long-term controlled studies, the angiotensin converting enzyme (ACE) inhibitors perindopril and trandolapril, the combined NEP (neutral endopeptidase)/ACE inhibitor omapatrilat, the angiotensin-receptor blockers (ARB) valsartan and olmesartan, and the aldosterone antagonist spironolactone had the capacity to reverse aortic stiffening independently of changes in BP.

Novel drugs in development, either aiming at antagonizing the deleterious effects of the renin-angiotensin system (AT2-receptor agonists, derivatives of angiotensin 1-7 and MAS agonists, activators of the angiotensin converting enzyme 2 - ACE2), at inhibiting advanced-glycation end products (AGE), or donating NO, are interesting compounds for a BP-independent destiffening of the arterial wall.